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Vitamin E supplementation and respiratory infections in older people

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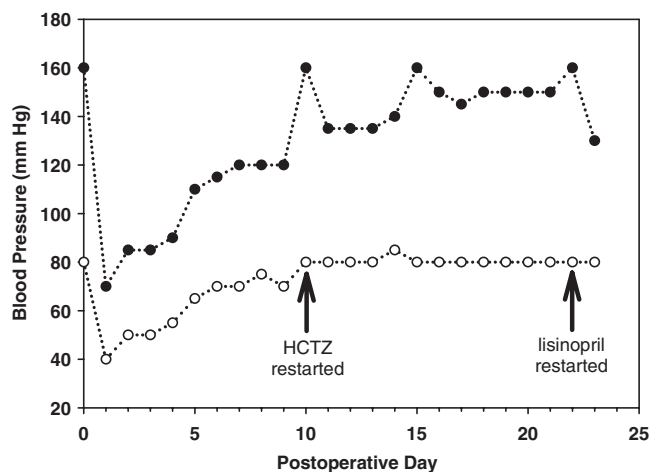


Figure 1. Systolic and diastolic blood pressure readings at baseline and during 3 weeks of postoperative follow-up. HCTZ = hydrochlorothiazide.

mechanism of hypotension after carotid endarterectomy may involve greater baroreceptor sensitivity. Baroreceptors are sensory receptors sensitive to stretch from increased pressure that function as part of a central reflex to reduce that pressure.¹ Baroreceptor reflex responses to carotid endarterectomy may involve removal of stiff atheromatous plaque, which improves arterial blood flow, allowing increased lateral pressure to be placed on the carotid artery lumen, which increases carotid sinus distension. The resultant stretching of the carotid sinus wall activates baroreceptors and a reflex response of heightened parasympathetic tone, thus inducing arterial vasodilatation, hypotension, and bradycardia.

Several observational studies have noted hypotension after carotid endarterectomy in the immediate postoperative setting that persisted weeks after surgery.^{2–5} Baroreceptor sensitivity after carotid endarterectomy has been evaluated using frequency domain analysis. One study demonstrated that peak increase in transfer function magnitude in the midfrequency region representative of baroreceptor activity may be consistent with heightened baroreceptor sensitivity after carotid endarterectomy.⁵ Author study showed decreases in blood pressure readings up to 5 years after carotid endarterectomy that may be a consequence of sustained increase in baroreceptor sensitivity.⁴ Baroreceptor sensitivity was estimated as the change in pulse interval in ms/mmHg change in blood pressure taken as an average after three maneuvers: Valsalva, angiotensin-induced vasoconstriction, and nitroglycerin-induced vasodilatation. Significantly lower systolic blood pressures were observed in patients with increased baroreceptor sensitivity in the postoperative period and at 5-year follow-up. Significantly diminished systolic and diastolic blood pressure ranges were also observed in patients with increased baroreceptor sensitivity in the postoperative period and at 5-year follow-up.

It is possible that our patient's initial hypotension after carotid endarterectomy and the subsequent moderation of hypertension severity, as suggested by fewer antihypertensive medicines being required, may be the consequence of greater baroreceptor sensitivity. If the increase in baroreceptor sensitivity is sustained, carotid endarterectomy may

offer a potential secondary benefit of long-term improvement in hypertension and blood pressure variability in addition to the primary goal of lowering stroke risk. Furthermore, in the acute period after carotid endarterectomy, geriatricians should be aware of the potential for baroreceptor-mediated hypotension as vigilant blood pressure monitoring and titration of antihypertensive medication may become essential.

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VITAMIN E SUPPLEMENTATION AND RESPIRATORY INFECTIONS IN OLDER PEOPLE

To the Editor: I read with great interest the Liu et al.¹ study examining the effect of multivitamin and mineral supplementation on infections in nursing home residents, although no rationalization for the supplement composition was described. In the large-scale Alpha-Tocopherol, Beta-Carotene (ATBC) Study with male smokers aged 50 to 69 at baseline, 20 mg/d β -carotene increased mortality² and had no effect on common cold incidence in 2,005 participants aged 65 and older³ or on pneumonia incidence in 2,985 participants aged 65 and older.⁴ Therefore, the inclusion of 16 mg/d of β -carotene in the supplement¹ would call for an explicit motivation, and the previous negative results should have been cited. In our further analysis of common cold incidence in the ATBC Study cohort, we found interaction between vitamin E and β -carotene supplementation (unpublished data), and therefore we restricted the more-detailed vitamin E analysis to participants who were not administered β -carotene.⁵

Table 1. The Effect of Vitamin E Supplementation on the Incidence of Respiratory Infections in Older People

Study (ref.)	Vitamin E Dose (mg/d)	Age	Person-Years	Outcome	Risk Ratio (95% Confidence Interval)	Subgroup; Notes
Hemilä et al. 2002 ³	50	≥ 65	8,020	Common cold	0.95 (0.90–1.00)	
Hemilä et al. 2006 ^{5*}	50	72–77	393	Common cold	1.58 (1.23–2.01)	≥ 15 cigarettes/d; out of cities
			444		1.35 (1.03–1.76)	≥ 15 cigarettes/d; city dwellers
			225		0.90 (0.63–1.28)	<15 cigarettes/d; out of cities
			176		0.54 (0.37–0.80)	<15 cigarettes/d; city dwellers
Meydani et al. 2004 ⁶	200	≥ 65	539	URI	0.88 (0.73–1.05)	Table 3 (ITT)
				Common cold	0.83 (0.68–1.01)	Table 3 (ITT)
Liu et al. 2007 ¹	44	≥ 65	929	URI	0.92 (0.75–1.12)	
Graat et al. 2002 ⁷	200	≥ 60	787	URI + LRI	1.12 (0.88–1.25)	
Harman & Miller 1986 ⁸	200–400	≥ 70 (77%)	51	LRI	1.07 (0.68–1.68)	Aged 24–104; 23% aged <70
Hemilä et al. 2004 ⁴	50	≥ 65	16,117	Pneumonia	0.94 (0.70–1.24)	
Hemilä et al. 2006 ^{9,10}	50	≥ 60	3,704	Pneumonia	0.08 (0.01–0.61)	Exercising during leisure
Meydani et al. 2004 ⁶	200	≥ 65	539	LRI	1.00 (0.80–1.26)	Table 3 (ITT)
Liu et al. 2007 ¹	44	≥ 65	929	LRI	0.91 (0.75–1.10)	

*Participants not administered β-carotene.

ITT = intention-to-treat analysis; LRI = lower respiratory infection; URI = upper respiratory infection.

Several trials examining the effect of vitamin E on respiratory infections in older people have been published (Table 1), yet Liu mentioned only the trial by Meydani et al.⁶ Another controlled trial⁷ with elderly Dutch people found no effect of vitamin E on the incidence of respiratory infections (Table 1), although vitamin E supplementation increased the number of symptoms ($P = .03$), the duration of illness ($P = .02$), the percentage of participants with fever ($P = .009$), and restriction of activity ($P = .02$). Thus, vitamin E may be harmful for some elderly people.

Other recent findings also suggest that vitamin E supplementation may be harmful. In the ATBC Study cohort, the effect of vitamin E on the incidence of the common cold diverged in older people.⁵ In participants aged 72 and older, vitamin E increased the risk of getting the common cold 58% in those who smoked heavily and did not live in cities, whereas it reduced common cold risk 46% in city dwellers who smoked less. The confidence intervals of these two subgroups are spectacularly far from each other (Table 1). Thus, there is strong evidence that older people are heterogeneous with regard to the effects of vitamin E on incidence of the common cold.

In the ATBC Study cohort, the age of smoking initiation significantly modified the effect of vitamin E on pneumonia incidence, indicating heterogeneity in the effects of the vitamin.⁴ In a subgroup analysis, we also found that vitamin E reduced the risk of pneumonia in participants who exercised in their leisure time (Table 1). Such heterogeneity limits the possibility of generalizing findings of trials.

Furthermore, in Liu's Table 4,¹ the analysis of antibiotic treatment is inappropriate. Although we may assume that "antibiotic courses" are independent observations, "antibiotic days" definitely are not independent, because a course of antibiotics consists of approximately 10 days directly linked to each other. The authors should have used, for example, the t test to analyze whether the mean duration of antibiotic courses differed between the study groups. Thus, the small P -value in Liu's Table 4 is not valid.

Finally, Liu refers to Chandra's 1992 report¹¹ without noting that a later publication, based on the same 1992 cohort, was retracted because of data fabrication,^{12,13} and serious doubts about the original 1992 article were also expressed because of various statistical inconsistencies.^{13,14}

Although vitamin E may affect the immune system in older people, the findings for clinical infections are mostly negative, and there is evidence of harm for some people. Therefore, vitamin E self-supplementation should be discouraged until those who might benefit from supplementation are identified accurately.

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RESPONSE LETTER TO DR. HEMILÄ

To the Editor: Dr. Hemilä raises the issue of the composition of the supplement used in our study, in particular the beta-carotene content, and he cites additional studies evaluating the effects of vitamin E. The composition of the multivitamin/mineral supplementation used in our study was chosen to meet or slightly exceed the Dietary Reference Intake for most nutrients. The literature available at the time of the planning of the study, including a study in which the validity has been seriously questioned, guided the composition of the supplement.¹ Nevertheless, other studies examining effects on infectious episodes have used formulations similar in composition to our intervention supplement.²⁻⁴ We also took into consideration the composition of commonly available over-the-counter vitamin and mineral supplementations.

We were aware of the association between beta-carotene and lung cancer in male smokers. We were also aware of a negative association between beta-carotene and lung cancer found in a study of 22,000 physicians.⁵ Several of the studies cited in Dr. Hemilä's letter are based on the same group of community-dwelling male smokers aged 50 to 69 from the Alpha-Tocopherol, Beta-Carotene Study.⁶ Although this is an important study, we question the generalizability and relevance of those results to our study population of older, mostly female, nonsmoking nursing home residents. The study by Graat et al.⁷ included older community-dwelling subjects, whereas our study focused on an institutionalized population, as did the Meydani publication.⁸ It was not our intention to provide a comprehensive review of papers published on vitamin E. Our study focused on the use of combination multivitamin and mineral supplementation, not specific micronutrients. The association between antioxidant supplementation and greater mortality has been documented in studies using doses higher than that provided in our study.⁹ Given the high rate of suboptimal intake of several nutrients (Table 5),¹⁰ including vitamin E (unpublished), the supplementation provided in our study would have served to bring subjects up to or just slightly above the daily required nutrient

intake, not into the range of high-dose supplementation. We thank the letter writer for pointing out two typographical errors in Table 4. We used Wilcoxon rank sum tests (*t* tests are not appropriate, because the outcomes were not normally distributed) to assess differences between the multivitamin supplementation and control groups for these secondary outcomes. For antibiotic days, the *P*-value in the second row should read .02.

Finally, we are aware of the concerns raised in the scientific community regarding authenticity of Dr. Chandra's work and indicated that his paper was considered "controversial" in our discussion. Despite the negative results reported in two recent meta-analyses,¹¹⁻¹³ the authors of those meta-analyses conclude that further studies are required, particularly in high-risk populations, such as nursing home residents. We believe that our study makes a worthy contribution in this area.

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